REMARKS

The Office Action

Claims 1-3, 23, 42-50, 52-55, 57-64, 69-75, and 77-82 are pending and examined in the present Office Action. Claims 47-50, 52-63, 69-75, and 77-84 are rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement. Claims 47-50, 52-63, 69-75, and 77-84 are further rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Claims 1, 3, 42, and 44 are rejected under 35 U.S.C. § 102(b). Claims 1-2 and 42-43 are also rejected under 35 U.S.C. § 102(b). Applicants address each of these rejections below.

Pending Claims

Claims 1-41 were submitted originally with the present patent application on July 27, 1998. Claims 4-22 and 28-41 were cancelled and claims 42-82 were added in a reply to Office Action mailed May 29, 2001. Claims 24-27 were cancelled in a reply to restriction requirement mailed January 22, 2004.

By the present claim amendments, claims 1-3 and 23 have been cancelled and new claim 83 has been added. Claim 42 has been amended to refer to an oligonucleotide encoding a polypeptide with formula $(P\text{-}K)_n$, where n is equal to 3, or more. Claim 43 has been amended to refer to an oligonucleotide encoding a polypeptide with formula $(P\text{-}K)_n$, where n is equal to 3, 4, 5, 6, 7, 8, 9, 10, or 15. In claim 46, the expression "formula (P-K)" has been deleted. In claim 47, the expression "having in its primary structure, tandem repeats which are rich in proline-type amino acid residues" has been added when referring to the plant protein reserve sequence. Finally, claims 75, 77, and 78 have been amended to refer to claims 54 and 47 in view of the withdrawal of claims 65-68. Support for these claim amendments can be found throughout the specification. For example, the amendment to claim 47 is supported in page 1, line 30 to page 2, line 1.

In the present Office Action, the Examiner rejected claims 47-50, 52-63, 69-75, and 77-84 under 35 U.S.C. § 112, first paragraph. Applicants note that, as claims 83 and

84 were not pending in the issuance of the present Action, the rejections of claims 83 and 84 are moot. Applicants address the remaining claim rejections accordingly.

Rejections under 35 U.S.C. § 112, first paragraph

Written description

Claims 47-50, 52-63, 69-75, and 77-82 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that "Applicants fail to describe structural features common to members of the claimed genus of polynucleotides encoding plant reserve proteins having P-K concantenations."

While Applicants do not agree with the Office's basis for the written description rejection, Claim 47 has been amended to include the expression "having in its primary structure, tandem repeats which are rich in proline type amino acid residues." As claims 48-50, 52-63, 69-75, and 77-82 depend on claim 47, Applicants respectfully request that the rejection be withdrawn for all claims.

Enablement

Claims 47-50, 52-63, 69-75, and 77-82 stand further rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner states that "the specification, while being enabling for Maize transformed with SEQ ID NO: 6, 8, or 10, does not reasonably provide enablement for any plant transformed and stably expressing any plant reserve protein." This rejection is respectfully traversed.

In rendering this objection, the Examiner purports that it would require undue experimentation to isolate and test the multitude of non-exemplified plant reserve protein sequences for addition of P-K concatenation to any number of domains for stable expression in a plant species other than maize. The legal criteria to be evaluated in an enablement rejection is based on the case of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d

1400, 1404 (Fed. Cir. 1998), which set forth several issues to evaluate undue experimentation:

1. *Nature of the invention and breadth of the claims*

The invention relates to a plant reserve protein sequence having in its primary structure, tandem repeats rich in proline residues, and in which is inserted an oligonucleotide encoding a P-K formula, resulting in a recombinant sequence. The expression of said recombinant sequence in a cell results in a recombinant protein having a localization and a structure (immunological recognizing by antibodies) similar to the natural (non-modified) plant reserve protein. Claim 47 contains sufficient features to construct such a recombinant sequence:

- the type of protein that has to be modified

  The protein is a plant protein reserve, and has to contain in its primary structure (amino acid sequence) tandem repeats rich in proline residues.

- the nature of the oligonucleotide to be inserted

  The oligonucleotides are characterized by their amino acid sequence (claims 42 and 44 to 46), by the presence of tandem P-K repeats and the presence of additional codons in 5' and 3'.

- the conditions of insertion of the oligonucleotides in the plant protein sequence

  Claim 47 specifies that the localization and the recognition by antibodies of the recombinant protein have to be the same as for the natural plant protein. These conditions restrict the possibilities of insertion of the oligonucleotide.

Thus, Applicants assert that the claims contain sufficient features, supported by the specification, to obtain the sequences, cells, and plants of the invention.

2. *The state of the prior art and level of predictability*

It is well known from the prior art that the insertion of a sequence in a protein may disturb the secondary (helix and sheet) and tertiary structures of a protein.

To avoid the perturbation of, or to reduce the consequences of such an insertion in the protein configuration, the skilled artisan knows that the sequence of the oligonucleotide to insert and that of the site of insertion need to have some similarities in terms of amino acid composition, type of interactions, and size of amino acid. Proline residues, because of their particular structure, induce distortions of approximately 20 degrees in the protein and have a restricted rotational freedom. As the oligonucleotide to insert encodes (P-K) repeats, the skilled artisan will choose a potential site of insertion whose primary structure (amino acid sequence) is similar to the structure of the sequence of the oligonucleotide.

Some of the sites of insertion, that can be chosen according to the conditions cited above (structure and localization), are described by the limitations of new claim 83.

The skilled artisan has basic knowledge concerning the modification of protein sequence and particularly site of insertion of foreign sequence to ensure a correct expression and localization.

3. *Relative skill of those in the art and quantity of experimentation necessary*

The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'

All steps, from plasmid construction to the determination of the expression and localization of the recombinant protein, are techniques regularly used without difficulty in labs of those skilled in the art to which the invention pertains.

- the plasmid construct (pages 19 to 22), and particularly the choice of vector, promoter (page 24), and use of restriction enzymes,
- the step of cell transformation, such as the calcium phosphate precipitation or the microprojectile bombardment (page 21-22),
- the determination of the correct expression of the recombinant protein with immunoblotting or gel analysis (page 22) techniques,
- the determination of the correct localization of the recombinant protein, using electron microscopy (page 23) or enzymatic test with a reporter gene (page 22).

Applicants assert that isolating and testing the recombinant constructs in the present invention do not require undue experimentation.

4. *Amount of direction or guidance presented and presence of working examples*

The specification provides several examples relating to both the site of insertion and the nature of oligonucleotides.

- place of insertion

Three places of insertion are reported in Figure 3: after the Pro-X or in place of the Pro-X (successful expression and localization) or N-terminal (unsuccessful experiment).

- nature of oligonucleotide

Figure 3 presents the oligonucleotides that are inserted in vectors, either one [P-K]$_4$K repeat in P20γZ or two [P-K]$_4$K repeats in H30γZ and H45γZ. From the specification and examples, the application discloses three sites of insertion and two types of oligonucleotides, 4 [P-K] repeats or 8 [P-K] repeats.

From the four vectors constructed (P20γZ, H30γZ, H45γZ, and N13γZ), three are efficient in recombinant protein localization and expression. The experiments made in or near the Pro-X domain were all successful (P20γZ, H30γZ, H45γZ), whatever the oligonucleotide sequence used.

Consequently, there is no reason to think that the insertion of claimed oligonucleotide containing $(P\text{-}K)_n$ repeats (with n equalling 3 or more), in appropriate place, in plant reserve protein sequence containing tandem repeat rich in proline, does not lead to the correct expression and localization of the recombinant protein.

For the reasons stated above, Applicants respectfully request that the enablement rejection of claims 47-50, 52-63, 69-75 and 77-82 be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1, 3, 42, and 44 are rejected under 35 U.S.C. § 102(b) for anticipation over Coupe et al. (*Plant Molecular Biology* 23(6):1223-1232 (1993); hereinafter "Coupe"). Claims 1 and 3 are cancelled. Applicants have addressed the rejection of claims 42 and dependent claim 44 by the amendment of claim 42.

Coupe teaches the following protein sequence, **P-K-P-K**-D-P-S-H-K-P-K-P-N-**P-K-P-K**-P, wherein it can be found two $[P\text{-}K]_2$ motifs (bold). However, Coupe fails to disclose a polynucleotide encoding a polypeptide with 3 or more consecutive (P-K) repeats. Claim 42 has been amended to refer to an oligonucleotide encoding a polypeptide with formula $(P\text{-}K)_n$, where n is equal to 3 or more. Thus, Coupe does not anticipate claim 42, as amended. As claim 44 depends on claim 42, Applicants request that the rejection under 35 U.S.C. § 102(b) in view of Coupe be withdrawn for claims 42 and 44.

Claims 1, 2, 42, and 43 stand rejected under 35 U.S.C. § 102(b) for anticipation over Forney et al. (*Mol. Cell. Biol.* 8(1):251-258 (1988); hereinafter "Forney"). Claims 1 and 2 are cancelled. The rejection of claims 42 and 43 is respectfully traversed.

M.P.E.P. § 2131 states:

> a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, described in a single prior art reference.

Applicants assert that Forney does not satisfy this standard for anticipation because it fails to describe each and every element of the rejected claims. Claim 42, from which claim 43 depends, requires "[a]n oligonucleotide comprising at least one concatenation coding for a polypeptide" (emphasis added). Forney discloses a nucleotide sequence from a telomeric region having G3T3 repeats, as mentioned on page 253, column 2 "the telomeric sequence consist of a combination of G4T2 and G3T3 repeats". However, Forney fails to disclose that these sequences encode a polypeptide. Rather, this sequence is involved in the addition of the telomeric region in ciliates, and, this region is not translated into amino acids to give rise to a polypeptide. Forney therefore fails to anticipate claims 42 and 43 since these claims refer to an oligonucleotide which transcribes a polypeptide with formula $(P\text{-}K)_n$. Applicants respectfully request that the rejection of claims 42 and 43 under 35 U.S.C. § 102(b) be withdrawn

CONCLUSION

Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested. Enclosed are a petition to extend the period for replying for two months, to and including September 20, 2004, and a check for $420.00 for the required petition fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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